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Review

The efficacy of Schwann cell transplantation on motor function recovery after spinal cord injuries in animal models: A systematic review and meta-analysis

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ABSTRACT

Aim: This article aimed to assess the efficacy of Schwann cell transplantation on motor function recovery in animal model of spinal cord injuries via meta-analysis.
Methods: An extended search was carried out in the electronic databases of Medline (via PubMed), EMBASE (via OvidSP), CENTRAL, SCOPUS, Web of Science (BIOSIS), and ProQuest. Finally, 41 eligible studies conducted on 1046 animals including 517 control animals and 529 transplanted animals were included in the meta-analysis. Pooled standardized mean difference (SMD) and odds ratio (OR) with 95% confidence interval (95% CI) were reported.
Results: The findings showed that treatment with Schwann cells leads to a modest motor function recovery after spinal cord injury (SMD = 0.85; 95% CI: 0.63–1.07; $p < 0.001$). Transplantation of these cells in acute phase of the injury (immediately after the injury) (OR = 4.30; 95% CI: 1.53–12.05; $p = 0.007$), application of mesenchymal/skin-derived precursors (OR = 2.34; 95% CI: 1.28–4.29; $p = 0.008$), and cells with human sources are associated with an increase in efficacy of Schwann cells (OR = 10.96; 95% CI: 1.49–80.77; $p = 0.02$). Finally, it seems that the efficacy of Schwann cells in mice is significantly lower than rats (OR = 0.03; 95% CI: 0.003–0.41; $p = 0.009$).
Conclusion: Transplantation of Schwann cells can moderately improve motor function recovery. It seems that inter-species differences might exist regarding the efficacy of this cells. Therefore, this should be taken into account when using Schwann cells in clinical trials regarding spinal cord injuries.

Contents

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1. Introduction

In recent years, cell therapy has been considered as a promising method in treatment of spinal cord injuries (Hosseini et al., 2015). Although multiple sources have been proposed for the transplanted cells, Schwann cells have always been regarded as one of the best candidates for this treatment (Kanno et al., 2014; Pearse et al., 2004a, 2004b; Takami et al., 2002). Schwann cells are responsible for neural protection and myelination in peripheral nervous system and normally they are not found in central nervous system. After injury, these cells migrate to the site of the lesion through the dorsal root and help the recovery to some extent. Studies suggest that application of Schwann cells can lead to a better recovery of sensory and motor function after spinal cord injuries (Kanno et al., 2014; Takami et al., 2002). However, a considerable number of surveys have yielded contradictory results (Barakat et al., 2005; Maldonado et al., 2006; Pearse et al., 2004b).

Recently, two meta-analyses, including data from 14 animal studies, proposed that transplantation of Schwann cells can significantly improve recovery of motor function in rats after spinal cord injuries (Lu et al., 2015; Yang et al., 2015a). However, presence of some limitation such as performing inefficient search, using unrelated keywords, and being subject to publication bias warrants the need for a redo of this meta-analysis. In this regard the present study aimed to re-evaluate the efficacy of Schwann cells in motor function recovery after spinal cord injury through a meta-analytic systematic review.

2. Methods

2.1. Search strategy

In this study, an extended search was carried out in the databases of Medline (via PubMed), EMBASE (via OvidSP), CENTRAL, SCOPUS, Web of Science (BIOSIS), and ProQuest, from 1 June 1946 until the end of September 2015. Search strategy was designed based on combining keywords related to “Schwann-like” and “Schwann cells” with terms related to “spinal cord injury” (Table 1). The keywords were selected based on three methods: a) from the Mesh and EMTREE terms; b) based on manual search in the titles and abstracts of the related articles; and c) through consultation with two specialists.

Findings from PubMed Central were also included when the PubMed database was searched. Moreover, non-indexed reports were also searched in Google search engine and Google scholar. The authors of the related articles were also asked to provide any unpublished data, information that is not registered or unpublished dissertations, if possible. The ProQuest database was also precisely searched for related theses. In cases where data were not available online, the corresponding author of article was contacted. A reminder was also sent to the author after one week of no response. If no answer was received, the co-authors were contacted through social networks such as ResearchGate and LinkedIn.

In order to find further studies and unpublished data, hand-search was carried out in the bibliography of relevant studies which yielded two more articles. Furthermore, hand-searching of journals was also performed. The articles were imported into EndNote X7 software and then a list of highly focused journals was created which included journals that had published the highest number of articles in the fields of stem cell therapy, neuroscience and spine. All the issues of these journals were manually searched and three more articles were found for inclusion in the meta-analysis.

2.2. Inclusion criteria

In the present study controlled animal surveys were included, in which the efficacy of Schwann cells in recovery of motor function after spinal cord injury was evaluated in rat and mice. Studies in which the cells were changed or modified in order to increase their efficacy were excluded. Genetic modification for cell labeling was not considered as an exclusion criterion. A follow up of less than 4 weeks was another exclusion criterion since the minimum duration of time needed for the cell therapy to take effect is three to four weeks. Surveys lacking control groups (sham, saline treated, or vehicle treated groups) were also excluded. Since the authors had aimed to evaluate the net effect of Schwann cells in recovery of motor function, the studies that had used co-treatments with these cells were also left out.

Table 1
Keywords used for search in databases of MEDLINE and EMBASE.

Database	Search terms
Medline (PubMed)	(Schwann Cells[mh] OR Schwann Cell*[mh] OR Schwannomas[tiab] OR Schwann*[tiab] OR Schwann-Like Cell*[tiab] OR SCs[tiab] OR SCs[tiab]) AND (“Spinal cord injuries”[MeSH] OR Spinal cord contusion[tiab] OR Spinal cord transection[tiab] OR Injured spinal cord[tiab] OR Spinal Cord Traum*[tiab] OR Spinal cord Hemisection[tiab] OR Spinal compression[tiab] OR Traumatic Myelopath*[tiab] OR Spinal Cord Laceratio*[tiab] OR Post-Traumatic Myelopath*[tiab])
EMBASE (OvidSP)	exp Schwann Cells/OR (Schwann Cell$ OR Schwannomas OR Schwann$ OR Schwann-Like Cell$ OR SCs).ti,ab. AND exp Spinal cord injuries/OR (Spinal cord contusion OR Spinal cord transection OR Injured spinal cord OR Spinal Cord Traum$ OR Spinal cord Hemisection OR Spinal compression OR Spinal Cord Laceratio$).ti,ab.

2.3. Quality assessment and data extraction

The findings of our searches were combined and the duplicate articles were removed via EndNote (version X7, Thomson Reuters, 2011). Two authors (M.Y and S.S) independently evaluated the titles and abstracts of the articles and screened potentially eligible studies. Subsequently, full-texts of these articles were studied and the ones that met the inclusion criteria were selected. Data were recorded in a checklist designed based on the guidelines of PRISMA statement (Moher et al., 2009). Extracted data included a) information related to characteristics of the animals, b) method of spinal cord injury induction, c) cell therapy protocol, d) follow up duration, e) evaluated outcome, and f) possible biases. Two reviewers assessed methodology of potentially relevant articles (93% agreement). In cases of disagreement between the two reviewers, a third person (A.MJ) evaluated the articles and the problem was solved through discussion with the two authors. Quality assessment of the studies was performed via the method suggested by Antonic et al. (Antonic et al., 2013).

2.4. Data synthesis

The target outcome in the present study was motor function recovery. Data were recorded as means and standard errors. Since the results were given as charts in most of these surveys, the method of data extraction from charts, proposed by Sistrom and Mergo, (Sistrom and Mergo, 2000) was used. The last evaluation of motor function recovery was included in the study. In cases where repetitive results were given, the study with the largest sample size and the longest follow up duration was included.

2.5. Statistical analysis

Data were summarized into mean and standard deviation figures and were entered into STATA 11.0 software. For each individual comparison, a standardized mean difference (SMD) was calculated with a confidence interval of 95% (95% CI), based on Hedges' g. Then a pooled effect size was presented. Evaluation of publication bias was done through drawing a funnel plot using the Egger's and Begg's tests (Egger et al., 1997). Heterogeneity between the studies was assessed via Chi-Squared and I^2 tests and a p value of less than 0.1 along with an I^2 greater than 50% were considered as presence of heterogeneity. Fixed effect model was utilized if the studies were homogenous, and if not, subgroup analysis was performed to find the source of heterogeneity. Random effect model was fitted for cases with no apparent source of heterogeneity. Subgroup analysis was carried out based on animals' gender, recipient species, injury model, location of injury, severity of injury, stem cells derivation origin, intervention phase (acute, subacute, chronic), graft type (allogeneic, xenogeneic), number of transplanted cells, donor species, use of co-treatment, antibiotic and immunosuppressive agents use, and blinding of the observer. Finally a meta-regression was performed in order to find the factors that influence the efficacy of Schwann cells in motor function recovery and odds ratio (OR) with a confidence interval of 95% were present. A p value of less than 0.05 was considered as statistically significant in all analyses.

3. Results

3.1. Characteristics of included studies

Search in electronic databases yielded 3409 non-repetitive records, from which 132 potentially eligible studies were identified and eventually 41 studies were included in the meta-analysis (Ban et al., 2011; Barakat et al., 2005; Barbour et al., 2013; Bunge, 2008; Firouzi et al., 2006; Flora et al., 2013; Garcia-Alias et al., 2004; Ghosh et al., 2012; Hill et al., 2012; Hu et al., 2013; Joghataei et al., 2010; Kamada et al., 2011, 2005; Kanno et al., 2014; Lavdas et al., 2010; Li et al., 2012; Madigan et al., 2014; Maldonado et al., 2006; Marcol et al., 2015; Moradi et al., 2012; Niapour et al., 2012; Papastefanaki et al., 2007; Pearse et al., 2004a, 2004b, 2007; Peng

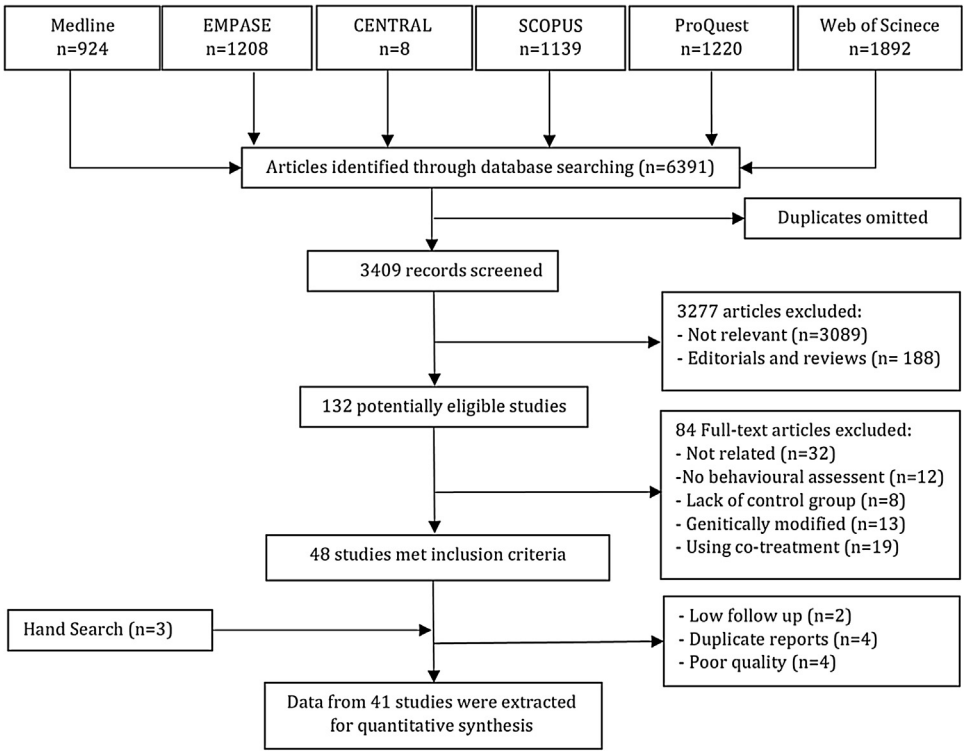

Fig. 1. Flowchart of including studies in the meta-analysis.

Table 2
Characteristics of included studies.

Author, Year	Gender/Species/ Weight	Model/Location of injury [a]/Severity	Cell source/Donor/Graft/Dose/Type/ Intervention time (day)	Immunosuppressive/ Antibiotic/Blinding	Follow up (day)
Ban et al. (2011)	Female/Rat/250–250	Contusion/T10/Moderate	Sciatic nerve/Rat/IS/3×10^6/Allogeneic/7	Yes/Yes/Yes	77
Barakat et al. (2005)	Female/Rat/180–200	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/56	No/Yes/No	56
Barbour et al. (2013)	Female/Rat/180–200	Contusion/T10/Moderate	Sciatic nerve/Rat/IS/5×10^5/Allogeneic/14	No/Yes/Yes	126
Bunge (2008)	Female/Rat/250–300	Compression/T9-T11/Moderate	Subcutaneous skin cells/Rat/IS/5×10^5/ Allogeneic/9	Yes/Yes/Yes	56
Firouzi et al. (2006)	Female/Rat/100–140	Compression/T10/Moderate	Sciatic nerve/Rat/IS/5×10^4/Allogeneic/7	No/Yes/Yes	70
Flora et al. (2013)	Female/Rat/180–200	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	84
Garcia-Alias et al. (2004)	Female/Rat/200–250	Photochemical/T8/Moderate	Sciatic nerve/Rat/IS/1.8×10^5/Allogeneic/1	No/No/Yes	90
Ghosh et al. (2012)	Female/Rat/180–200	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/No/Yes	56
Hill et al. (2012)	Female/Rat/190–196	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	70
Hu et al. (2013)	Female/Rat/160–180	Contusion/T10/Moderate	Sciatic nerve/Rat/IS/4×10^5/Allogeneic/9	Yes/No/Yes	42
Joghataei et al. (2010)	Male/Rat/250–300	Contusion/T8-T9/Moderate	Sciatic nerve/Rat/IS/3×10^5/Allogeneic/7	No/Yes/No	56
Kamada et al. (2005)	Male/Rat/200–200	Transection/T7-T8/Severe	MSC/Rat/IS/2×10^6/Allogeneic/1	Yes/Yes/No	42
Kamada et al. (2011)	Male/Rat/200–200	Contusion/T9/Moderate	MSC/human/IS/2×10^6/Xenogeneic/7	Yes/Yes/No	35
Kanno et al. (2014)	Female/Rat/160–180	Contusion/T8/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	84
Lavdas et al. (2010)	Female/Mice/20–25	Compression/T7-T9/Moderate	Sciatic nerve/Mice/IS/1×10^5/Allogeneic/1	No/No/Yes	28
Li et al. (2012)	Male/Rat/200–250	Contusion/T10/Moderate	Sciatic nerve/Rat/IS/9×10^4/Allogeneic/7	No/Yes/Yes	36
Madigan et al. (2014)	Female/Rat/230–250	Transection/T9/Severe	Sciatic nerve/Rat/IS/2.38×10^5/Allogeneic/ 1	No/Yes/Yes	28
Maldonado et al. (2006)	Female/Rat/180–220	Contusion/T10-T11/Moderate	Sciatic nerve/Rat/IS/5×10^5/Allogeneic/5	Yes/No/Yes	60
Marcol et al. (2015)	Male/Rat/300–300	Compression/T10/Moderate	Sciatic nerve/Rat/IT/9×10^5/Allogeneic/1	No/No/Yes	84
Moradi et al. (2012)	Male/Rat/250–280	Contusion/T10/Moderate	Sciatic nerve/human/IS/5×10^5/ Xenogeneic/7	Yes/Yes/Yes	56
Niapour et al. (2012)	Male/Rat/250–300	Contusion/T9-T10/Moderate	MSC/human/IS/5×10^5/Allogeneic/7	Yes/Yes/Yes	62
Papastefanaki et al. (2007)	Female/Mice/20–25	Compression/T7-T9/Moderate	Sciatic nerve/mice/IS/5×10^5/Allogeneic/1	No/No/Yes	28
Pearse et al. (2004a)	Female/Rat/160–180	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	84
Pearse et al. (2004b)	Female/Rat/160–180	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	56
Pearse et al. (2007)	Female/Rat/180–200	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	63
Peng et al. (2015)	Female/Rat/200–250	Contusion/T8-T9/Moderate	Sciatic nerve/Rat/IV/3×10^6/Allogeneic/1	No/Yes/Yes	56
Pourheydar et al. (2012)	Female/Rat/250–300	Contusion/T8/Moderate	Sciatic nerve/Rat/IS/3×10^5/Allogeneic/7	No/Yes/Yes	56
Schaal et al. (2007)	Female/Rat/180–200	Contusion/C5/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	49
Sharp et al. (2012)	Female/Rat/160–180	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/Yes/Yes	63
Someya et al. (2008)	Male/Rat/225–250	Contusion/T8-T9/Moderate	Sciatic nerve/Rat/IS/5×10^5/Allogeneic/7	Yes/Yes/Yes	35
Someya et al. (2008)	Male/Rat/225–250	Contusion/T8-T9/Moderate	MSC/Rat/IS/5×10^5/Allogeneic/7	Yes/Yes/Yes	35
Sparling et al. (2015)	Male/Rat/300–500	Dorsolateral funiculus lesioning/ C4-C5/Moderate	Subcutaneous skin cells/Rat/IS/2×10^6/ Allogeneic/1	Yes/Yes/Yes	70
Takami et al. (2002)	Female/Rat/160–180	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/2×10^6/Allogeneic/7	No/No/Yes	70
Walker et al. (2015)	Female/Rat/200–250	Contusion/C5/Moderate	Sciatic nerve/Rat/IS/1×10^6/Allogeneic/7	No/No/Yes	70
Wang and Xu (2014)	Female/Rat/200–220	Contusion/T9/Moderate	Sciatic nerve/Rat/IS/1×10^6/Allogeneic/7	Yes/No/Yes	70
Yan-Wu et al. (2011)	Female/Rat/220–250	Transection/T9-T10/Severe	MSC/human/IS/1×10^6/Xenogeneic/3	No/Yes/Yes	81
Zaminy et al. (2013a)	Male/Rat/250–300	Hemisection/T9-T10/Severe	MSC/Rat/IS/1×10^6/Allogeneic/1	No/Yes/No	56
Zaminy et al. (2013b)	Male/Rat/250–300	Hemisection/T9-T10/Severe	MSC/Rat/IS/1×10^6/Allogeneic/1	No/Yes/No	56
Zhang et al. (2007)	Female/Rat/200–250	Transection/T10/Severe	Sciatic nerve/Rat/IS/1×10^6/Allogeneic/1	No/Yes/Yes	54
Zhang et al. (2010b)	Male/Rat/140–160	Hemisection/T8/Severe	Sciatic nerve/Rat/IS/1.5×10^5/Allogeneic/7	Yes/No/Yes	63
Zhang et al. (2010a)	Male and Female/Rat/ 140–160	Hemisection/T8/Severe	Sciatic nerve/Rat/IS/1.5×10^5/Allogeneic/7	Yes/No/Yes	63
Zhang et al. (2015)	Female/Rat/200–250	Contusion/T8-T9/Moderate	Sciatic nerve/Rat/IS/1×10^5/Allogeneic/1	No/Yes/Yes	54

[a] T: thoracic level; C: cervical level; IS: intra-spinal; IT: intrathecal; IV: intravenous.

et al., 2015; Pourheydar et al., 2012; Schaal et al., 2007; Sharp et al., 2012; Someya et al., 2008; Sparling et al., 2015; Takami et al., 2002; Walker et al., 2015; Wang and Xu, 2014; Yan-Wu et al., 2011; Zaminy et al., 2013a,b; Zhang et al., 2010a,b, 2015, 2007) (Fig. 1). Characteristics of these studies are presented in Table 2. It is worth mentioning that two experiments with separate protocols were extracted from one study (Someya et al., 2008).

Data gathered from 1046 animals, including 517 control subjects and 529 animals in the transplanted group were analyzed. 28 (68.29%) studies evaluated female animals, 12 (29.27%) surveys had included male subjects and 1 (2.44%) study assessed both sexes. Rats were included in 39 (95.12%) studies and 2 (4.88%) experiments had been conducted on mice. Spinal cord injuries were induced by contusion model in 26 (63.41%) studies, compression model in 5 (12.19%) surveys, transection model in 4 (9.76%), and hemisection model in 4 (9.76%) studies. Severity of injury was moderate in 33 (80.49) studies and it was severe in the remaining 8 (19.51%) surveys. The mean duration of time between induction of injury and cell transplantation was 6.6 ± 8.5 days (ranged from 1 to 56 days). Transplantation was carried out in acute phase in 12 (29.27%) studies (immediately after injury), in sub-acute phase in 27 (65.85%) studies (3–9 days), and in chronic phase in only 2 (4.88%) surveys (more than two weeks after the injury). Cells were transplanted through intra-spinal method (intra-lesion) in all the studies except two. Transplant was allogeneic in 38 (92.68%) studies and xenogeneic in 3 (7.32%) surveys. The number of transplanted cells varied from 4×10^5 to 2.2×10^7 per one kilogram of the animal's body weight.

3.2. Meta-analysis

In order to evaluate motor function recovery in the included studies, Basso, Beattie, and Bresnahan score test was used for rats and Basso Mouse Scale was utilized for mice. No publication bias was observed (Coefficient = 0.08; 95% CI: −0.34–0.50 p = 0.71) (Fig. 2). Calculation of pooled SMD showed that transplantation of Schwann cells lead to a moderate improvement in motor function recovery (Pooled SMD = 0.85; 95%CI: 0.63–1.07; $p < 0.001$; I2 = 62.4%). The results of this section are presented in Fig. 3.

As can be seen, a moderate heterogeneity was observed between the articles ($I^2 = 62.4\%$; $p < 0.001$) and so subgroup analysis was performed. Table 3 presents the findings of this analysis. The most important sources of heterogeneity were recipient species, injury model, location of injury, Schwann cells derivation origin, intervention phase, graft type, number of transplanted cells, and donor species. Accordingly, the efficacy of Schwann cell transplantation was found to be relatively higher in compression (SMD = 1.04; 95% CI: 0.58–1.49) and hemisection/transection (SMD = 1.28; 95% CI: 0.71–1.85) models compared to the contusion model (SMD = 0.70; 95% CI: 0.45–0.96). Moreover, application of Schwann cells had better effects in motor function recovery after thoracic injuries (SMD = 0.88; 95% CI: 0.64–1.12) compared to injuries of cervical region (SMD = 0.56; 95% CI: 0.10–1.02). The efficacy of Schwann cell transplantation was also found to be higher when the cells were derived from mesenchymal/skin-derived precursors cells (SMD = 1.64; 95% CI: 0.94–2.33), when transplanted in the acute phase (SMD = 1.40; 95% CI: 0.97–1.84), when the cells are derived from human sources (SMD = 1.52; 95% CI: 0.55–2.48), and when the observer was not blinded to the treatment groups (SMD = 1.65; 95% CI: 0.56–2.57).

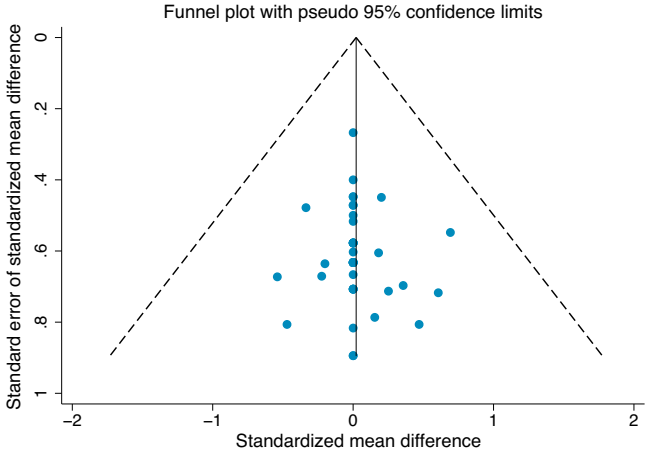

Fig. 2. Funnel plot for assessment of publication bias.

A meta-regression was performed to evaluate the independent effect of all these variables, in which all the factors were included in a regression model along with their effect size (Table 4). Accordingly, recipient species, donor species, and intervention phase were found to have influenced the efficacy of Schwann cell transplantation in recovery of motor function. The efficacy of these cells was found to be lower in mice (OR = 0.03; 0.003–0.41; p = 0.009) compared to rats. Schwann cells were found to improve motor function recovery to a greater extent, when the cells were derived from human sources (OR = 10.96; 1.49-80-77; p = 0.02). Cell therapy in the acute phase (OR = 4.3; 1.53–12.05; p = 0.007) also showed better results compared to sub-acute (OR = 1.63; 0.63–4.17; p = 0.29) and chronic phases. A significant increase in the efficacy was also observed when mesenchymal/skin-derived precursors Schwann cells were used instead of peripheral nerve derived Schwann cells (OR = 2.34; 95% CI: 1.28–4.29; p = 0.007).

4. Discussion

The present meta-analysis showed that transplantation of Schwann cells can induce a moderate motor function recovery after spinal cord injuries. Transplantation of these cells in the acute phase (immediately after injury) causes the efficacy to be twice the time when they are transplanted in the sub-acute of chronic phases (SMD = 1.40 vs. 0.67). Application of mesenchymal/skin-derived precursors Schwann cells (SMD = 1.64 vs.0.69) and cells with human sources (SMD = 1.52 vs. 0.79) also nearly doubled the efficacy of this treatment.

Lu et al. in a similar attempt conducted a meta-analysis in 2015, including 14 animal studies. They declared that Schwann cell transplantation can significantly improve motor function recovery in mice after spinal cord injuries, (Lu et al., 2015) while in the present study, only a moderate improvement was observed. The study conducted by Lu et al. had some important limitations. It was written in Chinese language, the authors only found 176 related non-repetitive articles in their systematic search and they included unrelated keywords for their search which is indicative of a weak search strategy that led to inclusion of only 14 studies in their meta-analysis. This increases the chance of publication bias in their survey. However, in the present study keywords were selected as extended as possible and more databases were searched. A great effort was paid to access gray literatures. This strategy led to screening of 6391 non-repetitive studies. Even after exclusion of surveys that had used co-treatments, 41 studies were included in the meta-analysis. Exclusion of these studies significantly decreased heterogeneity between the included articles ($I^2 = 62.4\%$) compared to that of Lu's survey ($I^2 = 82.2\%$). Moreover, no publication bias was observed in the present study. Application of an extended and more precise search strategy led to inclusion of more negative studies in our meta-analysis and so the efficacy of Schwann cells was found to be lower than that of reported by Lu et al. (Lu et al., 2015).

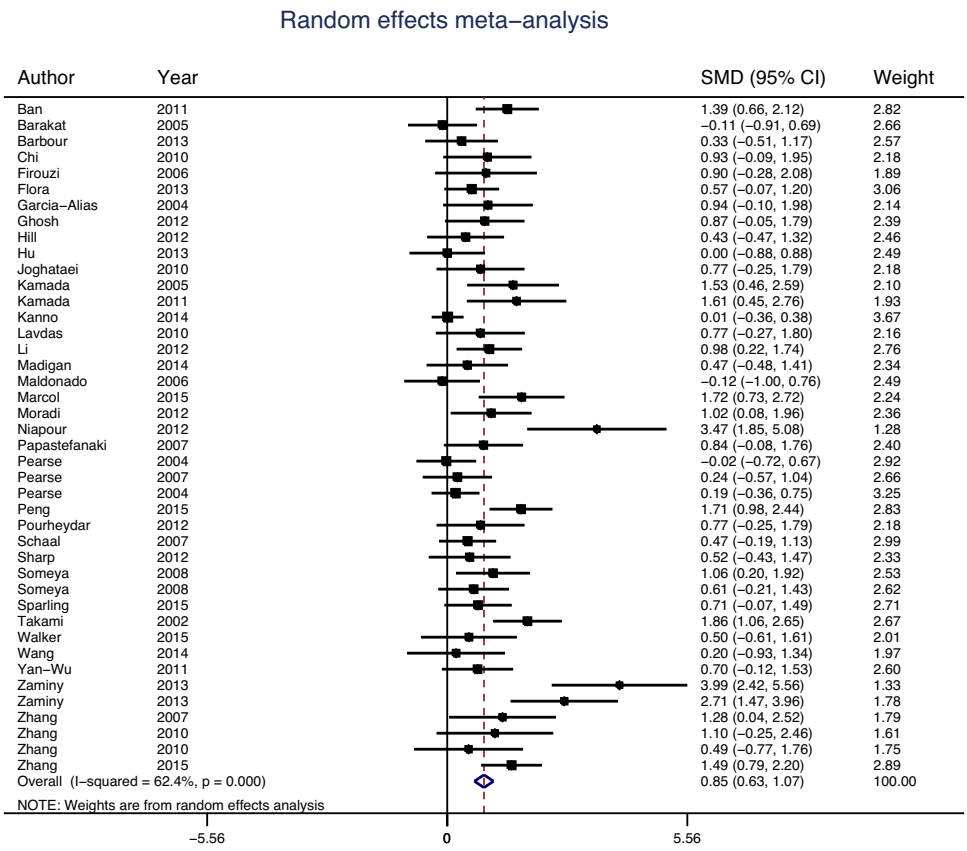

Fig. 3. Efficacy of Schwann cell transplantation on motor function recovery.

Another meta-analysis was done by Yang et al. in 2015. The study showed that Schwann cells have significant beneficial effects in motor recovery in various animal models of spinal cord injury (Yang et al., 2015b). However, there are major differences between the present study and Yang et al. study. The most important difference is in the search strategy of the studies. Searching in only one database in addition to Cochrane library, without searching in gray literature or doing hand search in Yang et al. study resulted in missing a large number of the articles and only 14 articles were evaluated in their meta-analysis. While, using an extensive strategy in the present study led to 41 articles entering the study. This resulted in major differences in the findings of the studies. For instance, Yang et al. study showed that Schwan cells are substantially beneficial regarding motor recovery in widely-used spinal cord injury animal models (SMD = 1.83). In contrast, the findings of the present study showed that improvement of motor function recovery after Schwann cell transplantation is only moderate (SMD = 0.85). In addition, in Yang et al. study some degrees of publication bias is seen ($P_{forEgger'sTest} = 0.087$), while in the present study, no publication bias is observed ($P_{forEgger'sTest} = 0.71$). Furthermore, the present study showed that there is no difference regarding effectiveness of stem cells between injury models, while Yang et al. study showed that Schwann cells have no effect on improvement of motor recovery in impact (contusion and compression) models, but lead to motor recovery of animals in hemisection model.

The moderate effect of Schwann cell transplantation in motor function recovery after spinal cord injuries could be attributed to the specifications of the injury and innate characteristics of Schwann cells. Although these cells are not found in the central nervous system, after spinal injury, due to inclusion of the dorsal root, Schwann cells migrate to the lesion site and induce myelination and axonal regeneration through their neuro-protective effects (Guest et al., 2005; Nagoshi et al., 2011). However, current evidence shows that during spinal injury, supra-spinal axons rarely regenerate in the site of lesion or at the site of Schwann cell transplantation and even the regenerated axons are not able to establish an effective connection with the spinal tissues (Chau et al., 2004; Golden et al., 2007; Takami et al., 2002). Accordingly, transplantation of Schwann cells at the site of spinal cord injury cannot significantly improve recovery of the motor function and that is why it is suggested by many studies that co-treatments should be used alongside transplantation to improve motor function recovery (Feng et al., 2005; Joghataei et al., 2010; Li et al., 2007; Maldonado et al., 2006; Pourheydar et al., 2012; Xia et al., 2013; Zeng et al., 2005; Zhang et al., 2010a).

Although the overall analysis of this study was indicative of a moderate efficacy, but application of Schwann cell transplantation in the acute phase was associated with doubling of the efficacy. This might be due to the protective role of Schwann cells in prevention and improvement of inflammatory processes. Although the environment around the site of lesion might be cytotoxic during the first hours after injury, presence of Schwann cells can induce release of growth factors which can stimulate the injured neurons for survival or axonal regeneration (Bixby et al., 1988). On the other hand, in sub-acute and chronic phases, the majority of axons are damaged and release of these growth factors cannot induce their effects. The findings of this study are congruent with the results of our previous meta-analysis, in which transplantation of bone marrow-derived mesenchymal cells was shown to exhibit higher efficacy in improvement of neuropathic pains after spinal cord injury when performed in the first 4 days after injury (Hosseini et al., 2015).

Table 3
Subgroup analyses of the effect of Schwann cell transplantation on motor function recovery.

	P for bias[a]	Model	P (I^2)[b]	Effect Size[c] (95% CI)	P
Gender					
Male	0.84	REM	0.002 (52.0%)	0.85 (0.63–1.07)	<0.001
Female	0.37	REM	0.001 (60.6%)	0.62 (0.41–0.85)	<0.001
Overall significance test among subgroups					<0.001
Recipient species					
Rat	0.95	REM	<0.001 (64.2%)	0.86 (0.63–1.09)	<0.001
Mice	0.99	FEM	0.92 (0.0%)	0.81 (0.12–1.49)	0.02
Overall significance test among subgroups					<0.001
Injury model					
Contusion	0.77	REM	< 0.001 (63.8%)	0.70 (0.45–0.96)	<0.001
Compression	0.64	FEM	0.67 (0.0%)	1.04 (0.58–1.49)	<0.001
Hemisection/Transection	0.35	FEM	0.44 (0.0%)	1.28 (0.71–1.85)	<0.001
Other	0.99	FEM	0.73 (0.0%)	0.80 (0.17–1.42)	0.013
Overall significance test among subgroups					<0.001
Location of injury					
Cervical	0.91	FEM	0.89 (0.0%)	0.56 (0.10–1.02)	0.02
Thoracic	0.73	REM	<0.001 (64.9%)	0.88 (0.64–1.12)	<0.001
Overall significance test among subgroups					<0.001
Severity of injury					
Moderate	0.79	REM	<0.001 (57.6%)	0.75 (0.53–0.97)	<0.001
Severe	0.43	REM	<0.001 (69.6%)	1.44 (0.70–2.18)	<0.001
Overall significance test among subgroups					<0.001
Schwann cells derivation origin					
Sciatic nerve	0.65	REM	0.001 (50.4%)	0.69 (0.48–0.90)	<0.001
Mesenchymal/skin derived cell	0.32	FEM	<0.001 (74.1%)	1.64 (0.94–2.33)	<0.001
Overall significance test among subgroups					<0.001
Intervention phase[d]					
Acute	0.55	REM	0.006 (57.9%)	1.40 (0.97–1.84)	<0.001
Subacute	0.75	REM	0.001 (50.4%)	0.67 (0.44–0.90)	<0.001
Chronic	0.99	FEM	0.46 (0.0%)	0.10 (−0.48–0.68)	0.74
Overall significance test among subgroups					<0.001
Graft type					
Allogeneic	0.79	REM	<0.001 (64.2%)	0.85 (0.61–1.09)	<0.001
Xenogeneic	0.29	FEM	0.46 (0.0%)	1.02 (0.47–1.56)	<0.001
Overall significance test among subgroups					<0.001
Number of transplanted cells					
$< 3 \times 10^6$ cell dose/kg	0.16	FEM	0.19 (22.7%)	0.72 (0.49–0.95)	<0.001
$\geq 3 \times 10^6$ cell dose/kg	0.39	REM	<0.001 (72.8%)	0.92 (0.61–1.24)	<0.001
Overall significance test among subgroups					<0.001
Donor species					
Rat	0.94	REM	<0.001 (63.0%)	0.79 (0.56–1.03)	<0.001
Mice	0.99	REM	0.02 (68.5%)	0.81 (0.12–1.49)	<0.001
Human	0.41	FEM	0.92 (0.0%)	1.52 (0.55–2.48)	<0.001
Overall significance test among subgroups					0.95
Use of antibiotic					
No	0.11	REM	0.06 (43.2%)	0.78 (0.39–1.16)	<0.001
Yes	0.85	REM	<0.001 (67.5%)	0.89 (0.62–1.16)	<0.001
Overall significance test among subgroups					<0.001
Use of immunosuppressive agents					
No	0.97	REM	<0.001 (50.3%)	0.83 (0.56–1.10)	<0.001
Yes	0.62	REM	0.02 (66.7%)	0.90 (0.53–1.28)	<0.001
Overall significance test among subgroups					<0.001
Blinding of observer					
No	0.26	REM	<0.001 (83.1%)	1.65 (0.56–2.75)	0.003
Yes	0.78	REM	<0.001 (52.3%)	0.75 (0.55–0.96)	<0.001
Overall significance test among subgroups					<0.001

[a] Publication bias based on Begg's and Egger's test.
[b] Heterogeneity among studies.
[c] Standardized mean difference.
[d] Acute (immediately after injury), subacut: 3–10 days after injury; chronic: equal or more than 14 days. REM: Random effect model; FEM: Fixed effect, CI: Confidence interval; NA: Not applicable because of low number of included studies.

Table 4
Meta regression analyses of the effect of Schwann cell transplantation on motor function recovery.

Variable	Odds ratio	95% Confidence Interval	P
Gender			
Female	*Ref*	*Ref*	---
Male	1.55	0.89–2.70	0.11
Recipient species			
Rat	*Ref*	*Ref*	---
Mice	0.03	0.003–0.41	0.009
Injury model			
Contusion	*Ref*	*Ref*	---
Compression	1.07	0.45–2.56	0.86
Hemisection/Transection	0.37	0.11–1.25	0.11
Other	0.92	0.12–3.34	0.22
Severity of Injury			
Moderate	*Ref*	*Ref*	---
Severe	2.07	0.66–6.58	0.21
Location of injury			
Thoracic	*Ref*	*Ref*	---
Cervical	0.84	0.39–1.81	0.65
Stem cells derivation origin			
Sciatic	*Ref*	*Ref*	---
Mesenchymal/skin derived cell	2.34	1.28–4.29	0.008
Donor species			
Rat	*Ref*	*Ref*	---
Human	10.96	1.49–80.77	0.02
Intervention phase [a]			
Chronic	*Ref*	*Ref*	---
Subacute	1.63	0.63–4.17	0.29
Acute	4.30	1.53–12.05	0.007
Graft type			
Allogeneic	*Ref*	*Ref*	---
Xenogeneic	0.54	0.01–1.09	0.06
Number of transplanted cells			
$<3\times10^6$ cell dose/kg	*Ref*	*Ref*	---
$\geq3\times10^6$ cell dose/kg	1.20	0.68–2.1	0.52
Use of immunosuppressive agents			
No	*Ref*	*Ref*	---
Yes	0.78	0.46–1.33	0.34
Use of antibiotic			
No	*Ref*	*Ref*	---
Yes	0.77	0.46–1.32	0.33
Blinding of observer			
No	*Ref*	*Ref*	---
Yes	0.79	0.36–1.76	0.56

[a] Acute (immediately after injury), subacut: 3–10 days after injury; chronic: equal or more than 14 days. Ref: Reference category.

The most common method for extraction and culture of Schwann cells is using peripheral nerves; however, recently some studies have used other sources including mesenchymal/skin-derived precursor Schwann cells. In these surveys, after differentiation to Schwann cells, they are transplanted at the site of spinal cord injury (Bunge, 2008; Kamada et al., 2011, 2005; Niapour et al., 2012; Someya et al., 2008; Yan-Wu et al., 2011; Zaminy et al., 2013a, 2013b). Subgroup analysis in the present study showed that in comparison with earlier derivation methods (from peripheral neurons), transplantation of mesenchymal/skin derived Schwann cells is associated with an increase in the recovery of motor function. This could be attributed to the modulation of inflammatory/immune responses by mesenchymal cells, since transplanted Schwann cells might be at different levels of differentiation and some might have preserved characteristics of mesenchymal cells (Urdzíková et al., 2014; Watanabe et al., 2015). Moreover, skin-derived Schwann cells are better at migration to the injured site and establishment of effective synaptic connections compared to peripheral nerves. These cells can modify the adjacent host tissue which can decrease gliosis (Biernaskie et al., 2007).

Application of human Schwann cells was another factor that increased efficacy of this treatment in motor function recovery. In four studies included in the meta-analysis, Schwann cells had human sources (Kamada et al., 2011; Moradi et al., 2012; Niapour et al., 2012; Yan-Wu et al., 2011), in three of which the Schwann cells were derived from mesenchymal stem cells (Kamada et al., 2011; Niapour et al., 2012; Yan-Wu et al., 2011). Therefore, the greater efficacy of human-derived cells might be caused by the anti-inflammatory and protective effects of mesenchymal cells rather than the Schwann cells (Singer and Caplan, 2011). Mesenchymal cells exhibit immunomodulatory effects (Alunno et al., 2014; Coulson-Thomas et al., 2014; Hou et al., 2014; Menendez et al., 2014; Montespan et al., 2014; Nauta and Fibbe, 2007; Wang et al., 2009) and when transplanted at a suitable time, they can minimize the inflammatory processes and damages caused by the immune system (Oudega and Ritfeld, 2014). Transplantation of these cells can decrease proliferation of glial cells and improve recovery by biologically active molecules through regulating release of cytokines and growth factors. Furthermore, their role in vascularization might induce generation of new vasculature in the spine (Hua et al., 2014; Kuchroo et al., 2014).

The results of the present study were also indicative of inter-species differences and efficacy of Schwann cell transplantation was found to be lower in mice, compared to rats (OR = 0.03). Although mice were only included in two studies, the differences cannot be ignored. The Lu et al. (Lu et al., 2015) and Yang et al. studies did not assess the inter-species differences of Schwann cell efficacy on motor function recovery after SCI. Therefore, comparison is not possible. Nevertheless, similar findings were also observed in our previous meta-analysis (Hosseini et al., 2015). Further investigations are required to confirm or reject the inter-species differences regarding treatment response to Schwann cell transplantation. If an inter-species difference exists regarding effectiveness of Schwann cells, more caution should be taken regarding using these cells in clinical trials. Therefore, it is suggested to evaluate the role of inter-species differences in effectiveness of Schwann cell transplantation in spinal cord injury recovery before carrying out any clinical trials.

The nature of this meta-analysis can be pointed out as one of the most important limitations of this survey. Due to their innate limitation in evaluating all the confounding factors, behavioral studies cannot definitely prove causal relationships. Although we tried our best to include studies with similar methodologies and controlling methods for confounding factors, but even in ideal situations these objectives cannot be reached. The presence of moderate heterogeneity was another limitation of this study which led the meta-analysis to be designed based on random effect model. In order to overcome this issue, subgroup analysis was performed which eliminated heterogeneity in 8 cases (Table 3).

5. Conclusion

Efficacy of Schwann cell transplantation in spinal cord injuries is evaluated in several studies, the results of which are somewhat incongruent. In this regard, we aimed to pool all these results in order to reach a consensus through a meta-analytic approach. The findings of this meta-analysis showed that transplantation of Schwann cells can moderately improve motor function recovery.

Finally it seems that inter-species differences might exist regarding the efficacy of this treatment protocol.

Conflict of interest statement

The authors report no declarations of interest.

Author contributions

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

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